

WHAT IS CLAIMED IS:

- Sub B2
1. An isolated expression vector comprised of (a) one or more silencer elements and one or more conditionally inducible elements to form a silencer-inducible region, and (b) a promoter in operative linkage with at least one silencer-inducible region, wherein said promoter is thereby regulated by said at least one silencer-inducible region, and upstream of at least one expressed region; said expression vector under an inducing condition expressing said at least one downstream region in an amount greater than expression of said at least one downstream region without said inducing condition.
 2. The expression vector of claim 1, wherein said promoter is a viral promoter.
 - Sub B3
 3. The expression vector of claim 1, wherein said promoter is a mammalian promoter active in several different tissues.
 4. The expression vector of claim 3, wherein said mammalian promoter is active in one or more different tissues selected from the group consisting of cardiac muscle, skeletal muscle, vascular endothelium, brain, retina, kidney, liver, lung, bone marrow, and spleen.
 5. The expression vector of claim 1, wherein said promoter is a cell-type specific promoter.
 - Sub B4
 6. The expression vector of claim 5, wherein said cell-type specific promoter is selected from the group consisting of cardiac muscle-specific promoters, skeletal muscle-specific promoters, endothelial cell-specific promoters, neuron-specific promoters, glia-specific promoters, retina-specific promoters, kidney-specific promoters, liver-specific promoters, lung-specific promoters, lymphocyte-specific promoters, myeloid-specific promoters, and tumor-specific promoters.
 7. The expression vector of claim 1, wherein at least one of said silencer elements is a neuron restrictive silencer (NRS) element bound by neuron restrictive silencer (NRS) transcription factor.

8. The expression vector of claim 1, wherein at least one of said silencer elements is a negative regulatory element (NRE) or repressor.

9. The expression vector of claim 1, wherein at least two of said silencer elements are present in genes selected from the group consisting of genes designated adenine nucleotide transporter-2, B29 (lg- β), CD95 (Fas/APO1), glutathione transferase P (GST-P), interferon- β (IFN- β), intestinal trefoil factor (ITF), lysozyme, metallothionein III (MT-III), testis specific histone H1t, thyroid hormone receptor- β 1 (TR- β 1), vascular cellular adhesion molecule-1 (VCAM-1), and von Willebrand factor (vWF).

10. The expression vector of claim 1, wherein at least two of said silencer elements are bound by transcription factors selected from the group consisting of CCTC binding factor (CTCF), goblet cell silencer inhibitor (SI), nuclear factor 1 (NF1) proteins, octamer binding proteins (Oct-1 and Oct-2), silencer factor A, and silencer factor B.

11. The expression vector of claim 1, wherein at least one of said conditionally inducible elements is a hypoxia response enhancer (HRE) element bound by hypoxia inducible factor-1 (HIF-1) transcription factor.

12. The expression vector of claim 11, wherein said HRE element is present in a gene selected from the group consisting of genes designated endothelin-1, enolase-1, erythropoietin, heme oxygenase, phosphoglycerate kinase, pyruvate kinase, and VEGF/Flt-1 receptor.

13. The expression vector of claim 11, wherein said HRE element is not bound by HIF-1 α including for example metallothionein I (MT-I) and metallothionein II (MT-II) bound by metallothionein transcription factor-1 (MTF-1).

14. The expression vector of claim 1, wherein at least one of said conditionally inducible elements is an oxidative stress response element.

15. The expression vector of claim 1, wherein at least one of said conditionally inducible elements is an anti-oxidant response element.

16. The expression vector of claim 1, wherein at least one of said conditionally inducible elements is selected from the group consisting of metal response elements (MRE), heat response elements, hormone response elements, and growth factor response elements.

17. The expression vector of claim 1, wherein at least one of said conditionally inducible elements is an NF- κ B responsive element bound by NF- κ B transcription factor.

18. The expression vector of claim 1, wherein said at least one expressed region is selected from the group consisting of functional coding regions of genes designated adenosine deaminase, angiopoietins, apoptosis inhibitor proteins, angiostatin, B-cell CLL/lymphoma (BCL2), catalase, deoxyribonuclease, DT-diaphorase, endostatin, erythropoietin, fibroblast growth factors (FGF), fumagillin, β -globin, glutathione peroxidase, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), heat shock transcription factor, hepatocyte growth factor (HGF), interferons, tissue metalloproteinase inhibitors, nitric oxide synthases, platelet derived growth factors (PDGF), proliferin, somatomedin C (IGF-1), superoxide dismutase, survivin, thymidine kinase, tissue plasminogen activator, tumor protein p53 (TP53), urokinase, and vascular endothelial growth factors (VEGF).

19. The expression vector of claim 1, wherein said at least one expressed region is selected from the group consisting of functional coding regions of reporter genes designated chloramphenicol transferase, green fluorescent proteins, red fluorescent protein, β -galactosidase, β -glucuronidase, β -lactamase, and luciferases.

20. The expression vector of claim 1, wherein said at least one expressed region is selected from the group consisting of functional portions of genes designated MDM2, tumor protein p53 (TP53), endothelin-1, tumor necrosis factors (TNFs), interleukins, interferons (IFNs), vascular endothelial growth factors (VEGFs), and other cytokines in the antisense orientation relative to said promoter.

21. The expression vector of claim 1, wherein at least one silencer element and at least one conditionally inducible element are heterologous with respect to each other in said silencer-inducible region.

22. The expression vector of claim 1, wherein at least one silencer element and one conditionally inducible element are arranged within 500 nucleotides of each other in said silencer-inducible region.

B7
conw
23. The expression vector of claim 1 which is a plasmid formulated for introduction into a cell by a technique selected from the group consisting of electroporation, naked DNA delivery, microinjection, and infusion.

24. The expression vector of claim 1 which is packaged as a replication defective adenovirus.

25. The expression vector of claim 1 which is packaged as an adeno-associated virus.

26. The expression vector of claim 1 which is packaged as a retrovirus.

27. The expression vector of claim 1 which is between 1000 and 50,000 nucleotides in length.

28. A genetically engineered cell or non-human organism containing the expression vector of claim 1 which was introduced into a host cell or non-human organism.

29. The genetically engineered cell or non-human organism of claim 28, wherein said host cell is a mammalian cell and said host organism is a non-human mammal.

30. A process of producing the expression vector of claim 1.

31. A process of using the expression vector of claim 1 comprising expressing said at least one downstream region by applying or having applied said inducing condition to said vector after transfer to a cell.

32. An isolated polynucleotide comprising a silencer-inducible region, which region comprises a silencer element and a conditionally inducible element, wherein the conditionally inducible element is operably linked to and heterologous to the silencer element, wherein operably linking the silencer-inducible region to a promoter provides for conditional silencing of transcription from the promoter.

33. The isolated polynucleotide of claim 32, wherein the silencer-inducible region is operably linked to a promoter.

34. The isolated polynucleotide of claim 33, wherein the promoter is a tissue-specific promoter.

35. The isolated polynucleotide of claim 32, wherein the promoter is heterologous to at least one of the silencer element or the conditionally inducible element of the silencer-inducible region.

36. The isolated polynucleotide of claim 32, wherein at least one silencer element and at least one conditionally inducible element are separated by no more than about 500 bases.

B

37. The isolated polynucleotide of claim 32, wherein the silencer element is selected from the group consisting of neuron restrictive silencer (NRS) elements and negative regulatory elements (NRE).

38. The isolated polynucleotide of claim 32, wherein the conditionally inducible element is selected from the group consisting of hypoxia response enhancer (HRE) elements, oxidative stress response elements, anti-oxidant response elements, metal response elements (MRE), heat response elements, hormone response elements, NF- κ B responsive elements, and growth response elements (e.g., SRF).

39. The isolated polynucleotide of claim 32, wherein the silencer-inducible region comprises at least two silencer elements.

40. The isolated polynucleotide of claim 32, wherein the silencer-inducible region comprises at least three silencer elements.

41. An expression vector comprising the polynucleotide of claim 32.

add B8

add D1